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Measuring appetitive conditioned responses in humans

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ABSTRACT

Clinical and preclinical findings suggest that individuals with abnormal responses to reward cues (stimuli associated with reward) may be at risk for maladaptive behaviors including obesity, addiction and depression. Our objective was to develop a new paradigm for producing appetitive conditioning using primary (food) rewards in humans, and investigate the equivalency of several outcomes previously used to measure appetitive responses to conditioned cues. We used an individualized food reward, and multimodal subjective, psychophysiological and behavioral measures of appetitive responses to a conditioned stimulus (CS) that predicted delivery of that food. We tested convergence among these measures of appetitive response, and relationships between these measures and action impulsivity, a putative correlate of appetitive conditioning. 90 healthy young adults participated. Although the paradigm produced robust appetitive conditioning in some measures, particularly psychophysiological ones, there were not strong correlations among measures of appetitive responses to the CS, as would be expected if they indexed a single underlying process. In addition, there was only one measure that related to impulsivity. These results provide important information for translational researchers interested in appetitive conditioning, suggesting that various measures of appetitive conditioning cannot be treated interchangeably.

1. Introduction

In classical appetitive conditioning, an initially neutral stimulus becomes associated with a rewarding unconditioned stimulus (US), such as food. This formerly neutral stimulus, now called the conditioned stimulus (CS), comes to elicit a conditioned response (CR), which often resembles the appetitive responses elicited by the US. Importantly, there is individual variation in the conditioned responses that emerge following appetitive conditioning, and this variation has been associated with the propensity to develop pathological behaviors including over-eating, addiction and depression [1–5]. For example, animals with heightened appetitive responses to CS associated with both drug and non-drug rewards (e.g. food) are at risk for certain addictive behaviors [6]. Similarly, obese individuals have heightened responses to CS that signal food reward [7,8]. Conversely, depressed patients show reduced activity in reward-related brain areas when viewing a CS previously paired with reward [9]. Together, these findings support the notion that differences in responses to appetitive CS may underlie reward-related pathological behaviors. The ability to consistently measure individual differences in appetitive conditioning in humans could help clinicians identify and develop treatment strategies for individuals with abnormal appetitive conditioning. However, the field lacks standardized, established ways to measure appetitive conditioned responses in humans. Two aspects of previously used paradigms are particularly problematic: use of secondary reinforcers that are themselves conditioned stimuli (e.g. money), rather than biologically significant primary reinforcers (e.g. food) as US, and use of non-standardized outcomes to measure the strength of appetitive responses to the CS.

While the human literature on aversive conditioning tends to utilize biologically significant US (i.e. painful shock, noise blasts, etc.) [10–14], the human literature on appetitive conditioning most often utilizes secondary reinforcers, such as money [11,13,15] and erotic pictures [16]. Secondary reinforcers engage different brain circuits than biologically significant primary reinforcers [11,17]. As the animal literature on appetitive conditioning generally uses biologically significant reinforcers (typically food), use of secondary reinforcers in the human literature raises questions about translational validity. The widespread use of secondary reinforcers may result from the difficulty of identifying universally-rewarding biologically significant US in humans [4]. There have certainly been studies utilizing food as a US in humans, but the majority of these have used sweets or chocolate

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[2,3,8,18–24], with only a few exceptions using a limited selection of reinforcers (e.g. one sweet or one savory snack) [10,25]. These studies have often pre-selected participants that prefer sweets [2,8,22], or populations presumed to prefer sweets, such as women [3,23,24]. This approach is problematic when the goal is to create a generally applicable measure of individual differences. Thus, the first goal of the current study was to test whether a novel paradigm that allowed individuals to select a preferred food from a wide variety of sweet and savory snacks could produce robust appetitive conditioning in humans to a biologically significant US without the need to pre-select participants.

A second issue with the appetitive conditioning literature in humans is the wide variety of measures of "appetitive responses" to the CS that have been used. These measures include subjective, behavioral, and physiological responses to the CS. Subjective liking of, attraction to, or arousal by the CS is typically measured through self-report, with appetitive CS typically rated as more positively valenced or arousing after conditioning [10,13,22,26–29]. Common behavioral measures of appetitive conditioning include approach tendency and attentional bias, with appetitive CS eliciting increased approach behavior and greater attention [13,26,30,31]. Appetitive CS can also elicit psychophysiological responses, which are typically measured by startle response suppression, skin conductance response, facial muscle responses via electromyography (EMG), and heart rate deceleration [10,16,18,32]. It remains to be determined whether or not these various multidimensional measures correlate with each other, or predict key external outcomes equivalently. Studies that have used several measures of appetitive conditioning have at times found inconsistent group-level (average) differences in the sensitivity of these measures to conditioning. For example, in one study a CS paired with appetitive food was rated as more positively valenced, yielded larger skin conductance response (SCR), and induced startle response attenuation [10], yet in another study a CS paired with sexual stimuli did not yield increased SCR [16]. In another example, a CS paired with food elicited a behavioral approach tendency, but not subjective craving [31]. However, these group-level, average differences do not directly address the question of whether various measures of appetitive conditioning correlate, as would be expected if they tap a unitary process or underlying individual difference in the strength of conditioned responses. To our knowledge, only one study has investigated relationships between appetitive responses to a CS, finding a correlation between electrophysiological responses to a CS and subjective ratings of that CS [19]. This lack of consideration for measure selection is problematic, because subjective, behavioral and psychophysiological responses often do not cohere in response to other emotional stimuli [33]. Thus, our second goal was to assess appetitive responses to the CS using a variety of outcomes, and test the extent to which appetitive responses to the CS on these various measures correlated with each other, and with a potential key external correlate, impulsivity. Impulsivity is thought to be related to increased sensitivity to appetitive rewards, and has been related to strength of appetitive conditioning in previous studies in both animals and humans [5,34–38].

Thus, our objective was to produce a robust and translational appetitive conditioning procedure in humans using food as a biologically significant US, and to use this procedure to examine the relationships between various measures of appetitive responses to the CS. We hypothesized that our individualized appetitive conditioning procedure would yield robust appetitive responses to the CS at a group-level (i.e. on average), across subjective, psychophysiological and behavioral measures. However, we had an open hypothesis about whether the various measures of appetitive response would be correlated with each other, and how they would relate to the external correlate of impulsivity.

2. Methods and materials

2.1. Participants

90 healthy volunteers (59 female, 31 male) ages 18 to 35 were recruited through flyers, online advertisements, and word of mouth. Participants first completed a brief eligibility survey online or by phone. If a participant appeared likely to qualify, they attended a 2 h in-person screening consisting of a review of their medical history, a modified structural Clinical Interview for DSM-IV [39], drug use history form, and the Barratt Impulsiveness Scale (see Section 2.4.2. Measures of Impulsivity). Exclusion criteria were: Serious medical condition, past year DSM-IV Axis I Disorder (except Substance Abuse), lifetime Substance Dependence, smoking > 10 cigarettes per week, psychoactive medications, pregnancy, less than high-school education or poor English fluency.

Prior to each session, participants were instructed to refrain from alcohol and over-the-counter drugs for 24 h, refrain from all recreational drugs for 48 h, maintain typical caffeine and nicotine intake for 24 h, and eat and sleep normally. Compliance with alcohol and drug requirements was verified using Alco-Sensor III breathalyzers (Intoximeters Inc., St. Louis, MO) and Readitest 6 Cassette urine drug screens (Redwood Toxicology, Santa Rosa, CA). Female participants completed a urine pregnancy test (Pro Advantage, National Distribution & Contracting, Inc., Nashville, TN) before each session. All participants provided informed consent, and all procedures were approved by the University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects and carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Overall design

The study consisted of two 2 h sessions (see Fig. 1). In Session 1, participants completed an orientation, provided baseline picture ratings to select the conditioned stimulus (CS) and control picture, completed the first conditioning session, and did post-conditioning manipulation checks. In Session 2, participants completed the second conditioning session, post-conditioning manipulation checks, measures of appetitive responses to the CS vs. the control picture ("Rating Pictures Task", "Chasing Pictures Task" and "Dot Probe Task", presented in counterbalanced order) and the Stop Signal Task measure of impulsivity. Sessions were conducted 48–96 h apart, during typical working hours (8 am–6 pm) and both were required to be at the same time of day (within a 1 h window).

2.3. Procedures

2.3.1. Session 1

Fig. 1 shows a timeline of both sessions. At the beginning of Session 1, baseline criteria were confirmed and participants rated their hunger on a visual analog scale from 0 "Not hungry at all" to 100 "As hungry as I've ever been". Psychophysiological sensors were then applied. Participants selected a preferred snack from a variety of savory and sweet snacks (Reese's Pieces, Peanut M&Ms, Gummie Bears, Cheez Its, Chex Mix, Pringles, microwave popcorn) and completed a brief orientation to the conditioning procedure and measures of appetitive responses using practice stimuli (these stimuli were never shown again). Participants then rated the subjective valence of 12 neutral pictures from −4 (very negative) to 4 (very positive) using the Evaluative Space Grid [40]. They rated the arousal of the same pictures using a one-item scale ranging from 1 (not at all arousing) to 9 (extremely arousing), per [41–43]. Two images with median valence ratings (typically 0 or 1) and the most similar arousal ratings were randomly assigned to be the CS and control picture. The control picture was not presented again until after conditioning.